IMGN632, a CD123-Alkylating ADC Bearing a DNA-Alkylating IGN Payload, Combines Effectively with Azacitidine and Venetoclax In Vivo, Prolonging Survival in Preclinical Models of Human Acute Myeloid Leukemia (AML)

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Background

IMGN632, a novel CD123-targeting ADC, demonstrates a favorable safety profile and complete remissions as a monotherapy in patients with relapsed refractory AML and BPDCN (NCT03386513). We have previously reported the synergy of combining IMGN632 with venetoclax (BCL-2 inhibitor) (EHA, 2019, abstract #PF201). Given the recent approval of azacitidine (AZA), a hypomethylating agent and venetoclax (VEN) in AML patients unfit for intensive chemotherapy, we investigated the combination of IMGN632 with AZA and the triple combination of IMGN632, AZA and VEN.

IMGN632 is a CD123 targeting Antibody-Drug Conjugate with a DNA alkylation payload

- IMGN632 is a novel CD123-targeting ADC
  - composed of a humanized IgG1 antibody with high affinity to CD123.
  - Highly potent payload, DGN549, alkylates DNA without cross-linking.
  - Linker is a peptide cleaved intracellularly and is stable in circulation.
  - Conjugation is site-specific via engineered cysteines.
  - Two payload molecules per antibody.

ADCs with DNA alkylator promote cell death

Antibody Drug conjugates (ADCs) with DNA alkylating payloads induce cell killing by:
1. Binding of ADC to the target cell and inducing internalization and uptake by the lysosomes.
2. The cytotoxic payload is released.
3. Payload alkylates DNA
4. Induction of apoptotic cell death

IMGN632 in combination with Azacitidine and Venetoclax induces cytotoxicity and apoptosis in MOLM-13 and MV4-11 cells

Anti-leukemic efficacy of the triple combination in pre-clinical models of AML

- Efficacy of the triple combination in three AML Patient-derived xenograft models (PDX)

Conclusion

- IMGN632 in combination with AZA and VEN improved survival in patient-derived xenograft (PDX) and multiple AML xenograft models.
- IMGN632 in combination with AZA and VEN induces apoptosis possibly by inducing p53 and upregulation of NOXA leading to apoptotic cell death.
- These data support the addition of IMGN632, a CD123 targeting ADC with a novel DNA damaging payload to standard of care AZA+VEN in AML patients.
- The combination of IMGN632 and Venetoclax and/or Azacitidine is currently being tested in a Phase 1/2 clinical trial (NCT04088264).